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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,326	05/11/2001	Toni Rita Prezant	18810-81401	7808

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,326	PREZANT ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-8 and 24-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 8-4-03 has been entered. Claims 1-3, 7 and 8 have been amended. Claims 9 and 10 have been canceled. Claims 24-31 have been added. Claims 1-8 and 24-31 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-8 remain rejected and claims 24-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing neoplastic transformation by PTTG1 polypeptide and the proline-rich domain of PTTG1 is important for PTTG-mediated neoplastic transformation, and overexpression of PTTG2 inhibits transactivation activity of PTTG1 by nearly half *in vitro*, does not reasonably provide enablement for a method of inhibiting neoplastic cellular comprising any expression vector expressing a mammalian PTTG2 peptide to a mammalian cell via any administration route *in vivo*, wherein said PTTG2 peptide consists essentially of amino acid residues 1-191 of SEQ ID No. 64 or a functional fragment thereof comprising at least 1-180 of SEQ ID No. 64, or a mammalian PTTG2 peptide having at least 95% identity to the PTTG peptide set forth above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in

the preceding Official action mailed 1-9-03. Applicant's arguments filed 8-4-03 have been fully considered but they are not persuasive.

Applicants cite exhibit A and argue that several human gene therapy clinical trials have been conducted and pre-clinical trials have had to be partially successful that required a large body of good reliable data on animal models and vectors for gene therapy (amendment, p. 11, 12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-03. The art of gene therapy in vivo remains unpredictable and not well-developed at the time of the invention. Each gene therapy in vivo has to be considered case by case and a successful gene therapy in vivo can not be extrapolated to success for another gene therapy in vivo. The protein encoded by the delivered polynucleotide, the biological function of said protein, the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy. Administration route of the vector or polynucleotide for gene therapy determines how those factors affect the success of said gene therapy in vivo. Therefore, one skilled in the art the time of the invention would required undue experimentation to practice over the full scope of the invention claimed.

Applicants cite exhibits B and C and argue that model of in utero gene therapy in large mammal and long-term in vivo therapeutic expression of exogenous genes and clinical improvement in a human suffering from adenosine deaminase deficiency are successful and that

the claimed method is not limited to any particular expression vector and can be practiced using a variety of available expression vectors (amendment, p. 12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-03 and the reasons set forth above.

Applicants cite exhibits D and E and argue that intravascular injection of pseudotyped retroviral vectors can target selective transduction of tumor cells in vivo within metastatic tumor foci and the use of tumor-specific promoter, such as HREs, was known (amendment, p. 13).). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-03 and the reasons set forth above. Although selective expression of the therapeutic gene in tumor cells was known in the art, however, other factors have to be considered for a successful particular gene therapy in vivo. Such factors include the biological function of the protein, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the stability of the protein produced, and whether sufficient amount of protein can be obtained at the target cells. The efficiency of gene transfer for a particular gene therapy in vivo depends on the therapeutic gene used, the vector used, and how the therapeutic gene being delivered.

Applicants cite exhibits F, G and H and argue that intraarterial delivery of HSV-1 mutant hrR3 vector + GCV or adenoviral vector + GCV to brain tumor results in tumor regression in rats and does not have host immune response problem (amendment, p. 13, 14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-03 and the

reasons set forth above. Each type of vector, such as adenoviral vector, AAV, vaccinia virus vector, herpes simplex virus vector, retrovirus vector, and plasmid etc, stimulates varying degrees of host immune response, especially adenoviral vector can stimulate strong host immune response that eliminates the polynucleotide delivered before it reaches target site. Further, the cited exhibits concern treating brain tumors with viral vectors but it was well known in the art that the brain is much more immunologically inert as compared to other parts of an individual and blood brain barrier poses a particular challenge for gene delivery to the brain via various administration routes. Thus, the claims remain rejected under 35 U.S.C. 112 first paragraph.

Applicants cite exhibit I and argue that intraarterial administration of hrR3 HSV-1 mutant vector in combination with immunosuppressant cyclophosphamide in immunocompetent rats does not have host immune response problem (amendment, p. 14, 15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-03 and the reasons set forth above.

Conclusion

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.